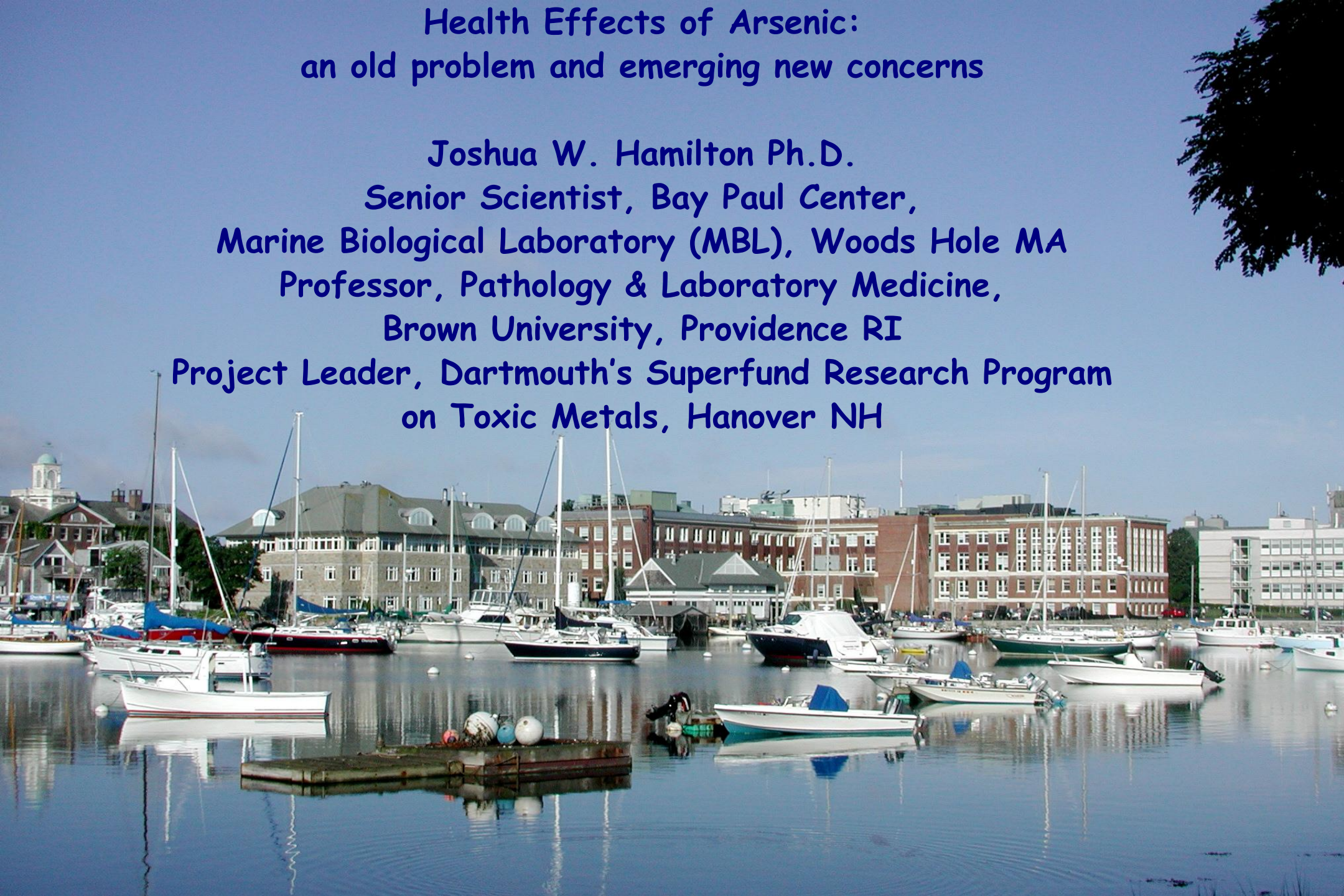


Health Effects of Arsenic: an old problem and emerging new concerns

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Arsenic and Old Concerns

“It is an uncanny thought that this lurking poison (arsenic) is everywhere around us, ready to gain unsuspected entrance to our bodies in the food we eat, the water we drink and the air we breathe.”

Karl Vogel, 1928

METALS:

Toxic Metals, Heavy Metals, Essential Metals

Periodic Table of the Elements

1A																	0		
1	H																	2	
2	Li	Be																	10
3	Na	Mg	III A	IV A	V A	VI A	VII A									18			
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr	
5	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe	
6	Cs	Ba	* La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn	
7	Fr	Ra	+ Ac	Rf	Ha	106	107	108	109	110									

58	59	60	61	62	63	64	65	66	67	68	69	70	71
Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
90	91	92	93	94	95	96	97	98	99	100	101	102	103
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

* Lanthanide Series
+ Actinide Series

- three-fourths of all elements are metals or metalloids
- a “heavy metal” refers to its atomic weight, not its toxicity
- many metals are essential or play a normal role in biology
- many toxic metals that are not essential can mimic essential metals
- like all chemicals, all metals are toxic at high enough doses
- like all chemicals, all metals are non-toxic at very low doses

Toxic metals in the environment

- Toxic metals are a major concern at both Superfund / toxic waste sites and in the environment in general
- Eight of the top fifty substances on the CDC's ATSDR priority list are metals, including the top three chemicals of concern in the environment: arsenic, lead and mercury
- Eight of the twenty-two substances on the EPA's OSWER list of chemicals of highest concern at Superfund sites are metals: arsenic, lead, mercury, cadmium, chromium, nickel, zinc and copper

Arsenic: “poison of kings and king of poisons”

- Ancient Rome - Women's club used arsenic to poison husbands
- Renaissance - The Borgias used arsenic to poison rivals and increase their wealth
- Were Napoleon and Mozart poisoned by arsenic?



Cesare Borgia

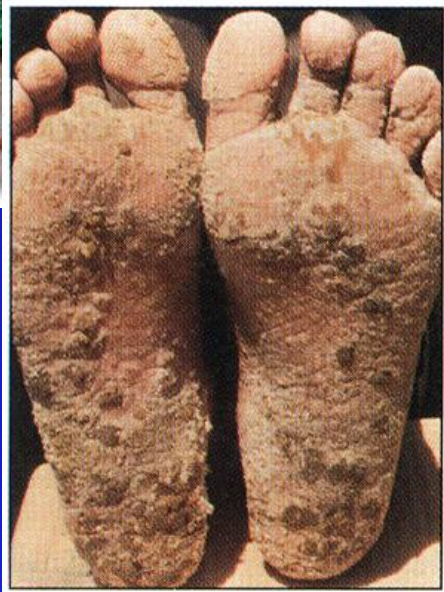
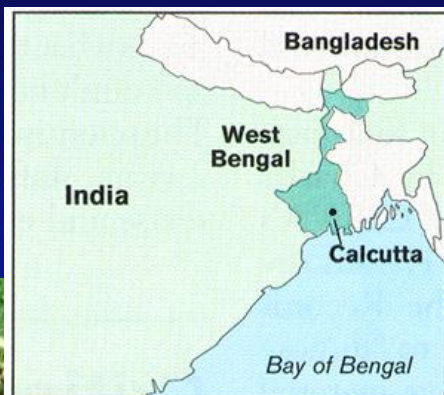


“The death of Napoleon”



a lock of Napoleon's hair

Arsenic as an environmental contaminant



- Previous US and WHO drinking water standard (Maximum Contaminant Level, MCL) for arsenic was 50 parts per billion (ppb) from 1950's through 2001
- US recently lowered MCL to 10 ppb (Jan. 2006), but 7-14 year implementation
- current WHO and EU arsenic standard is 10 ppb
- WHO program of digging tube wells in India, Bangladesh to alleviate cholera problem led to massive population exposure to excess arsenic in drinking water
- highly contaminated areas (India, South America) can contain as much as 1800 ppb (180 times the WHO standard)
- Estimated 250 million to 1 billion people affected worldwide by excess arsenic

Arsenic as a causative agent in human disease

- Chronic human exposure to inorganic arsenic at sub-acute doses has been linked to increased risk of:
 - Cancers- esp. lung, skin and bladder but also liver, kidney, and other malignancies
 - Diabetes (type 2, non-insulin-dependent, “adult-onset”)
 - Vascular and cardiovascular disease
 - Reproductive and developmental problems
 - Neurological problems
- U.S. & South America - range is typically 1-100 ppb
- Asia - range is typically 10-1000 ppb

Arsenic as an environmental contaminant in New England

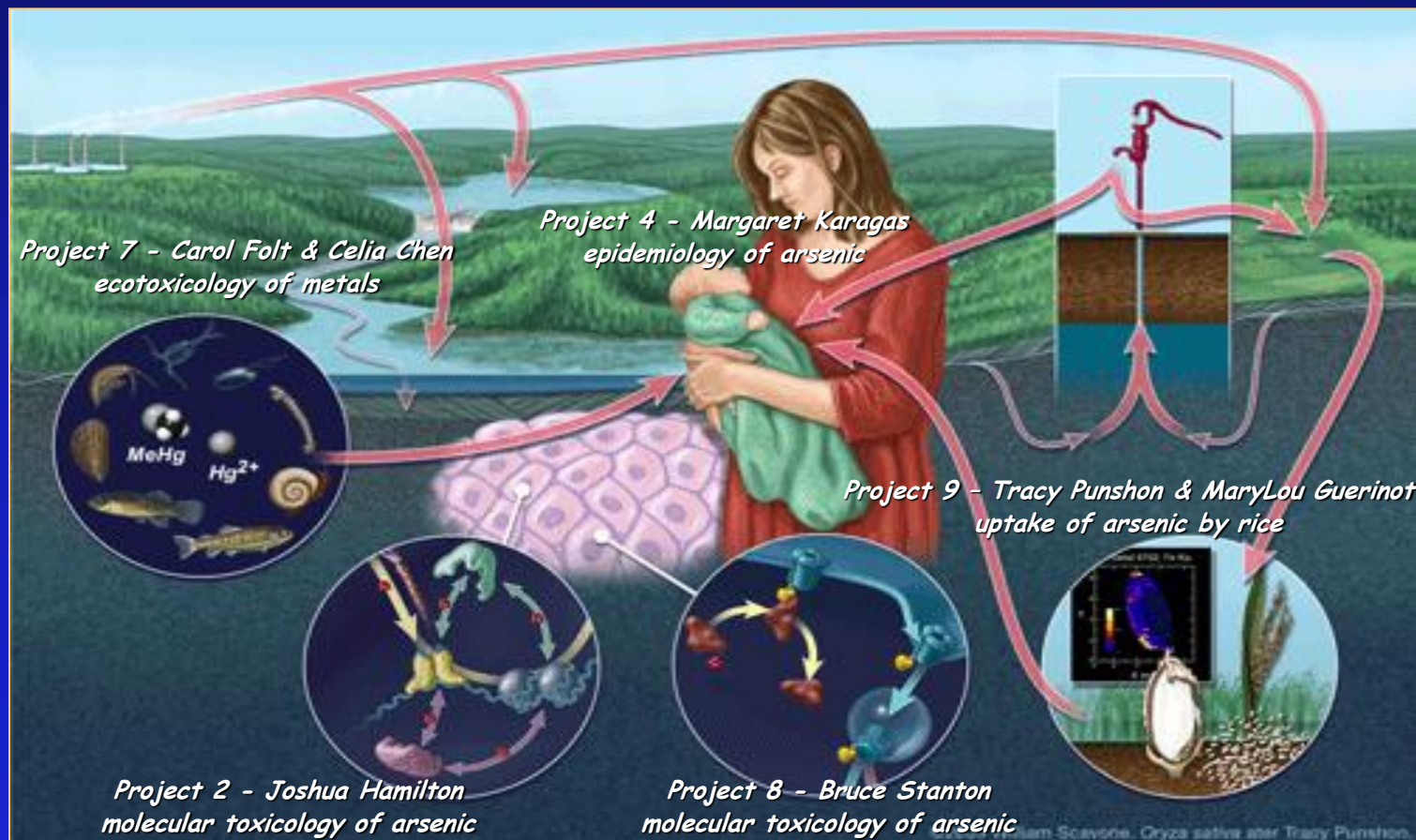


- In New Hampshire, ~40% of the population gets its drinking water from private, unregulated wells
- Of these wells, greater than one in five has excess arsenic, representing about 10% of the state's population (~120,000 people)
- Similar ratios are found in Maine (~150,000 people)
- In the U.S. as a whole, as many as 25 million people may be drinking excess arsenic in their drinking water
- NH and ME also have elevated levels of arsenic in soil both naturally and from lead arsenate pesticide use (avg. 20 ppm vs. 1-5 ppm in most of U.S.)



Center for Environmental
Health Sciences at Dartmouth

Dartmouth
TOXIC METALS
Research Program



“Toxic Metals in the
Northeast”
NIH-NIEHS Sponsored
Dartmouth Superfund
Basic Research Program
Project on Toxic Metals

An interdisciplinary
research program on
toxic metals in the
environment and their
impact on ecosystems and
human health

Arsenic as an endocrine disruptor

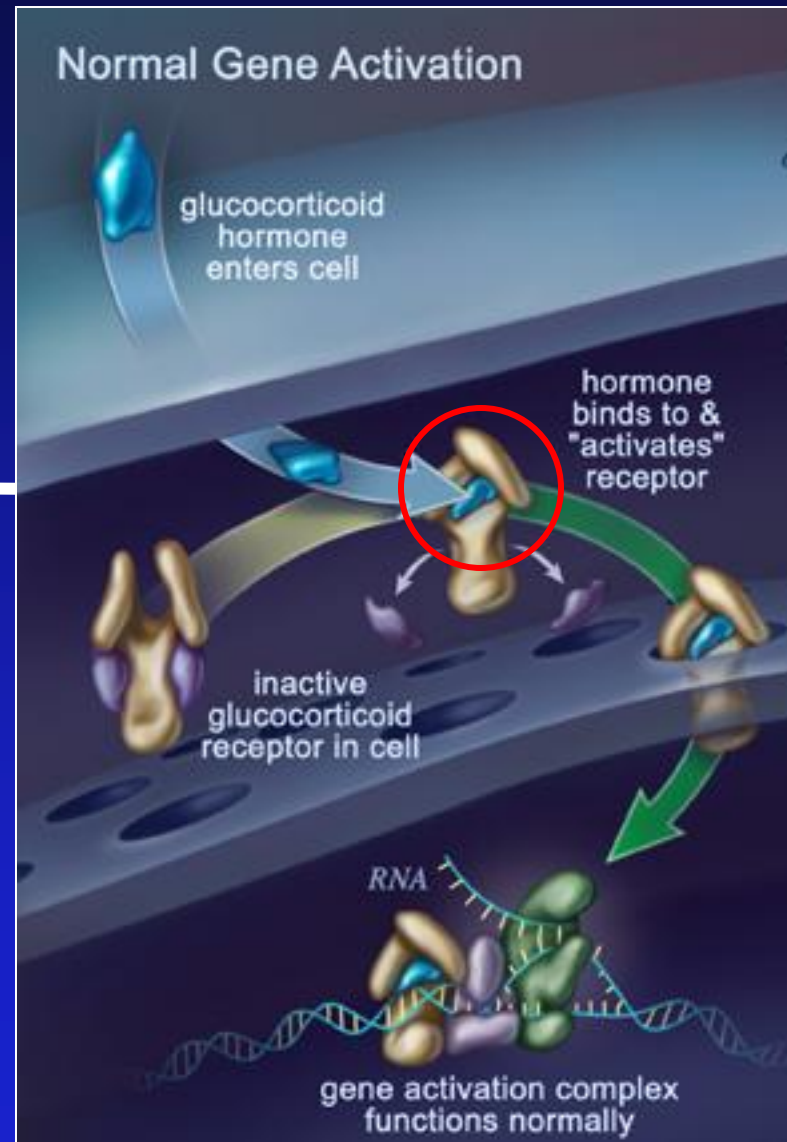
What is an endocrine disruptor?

“Collectively, chemicals with the potential to interfere with the function of endocrine systems are called endocrine disrupting chemicals (EDCs). EDCs have been defined as exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes.”

Strategic Research Plan for Endocrine Disruptors, 1998
Office of Research and Development
U.S. EPA

Hormone receptor biology and endocrine disruption

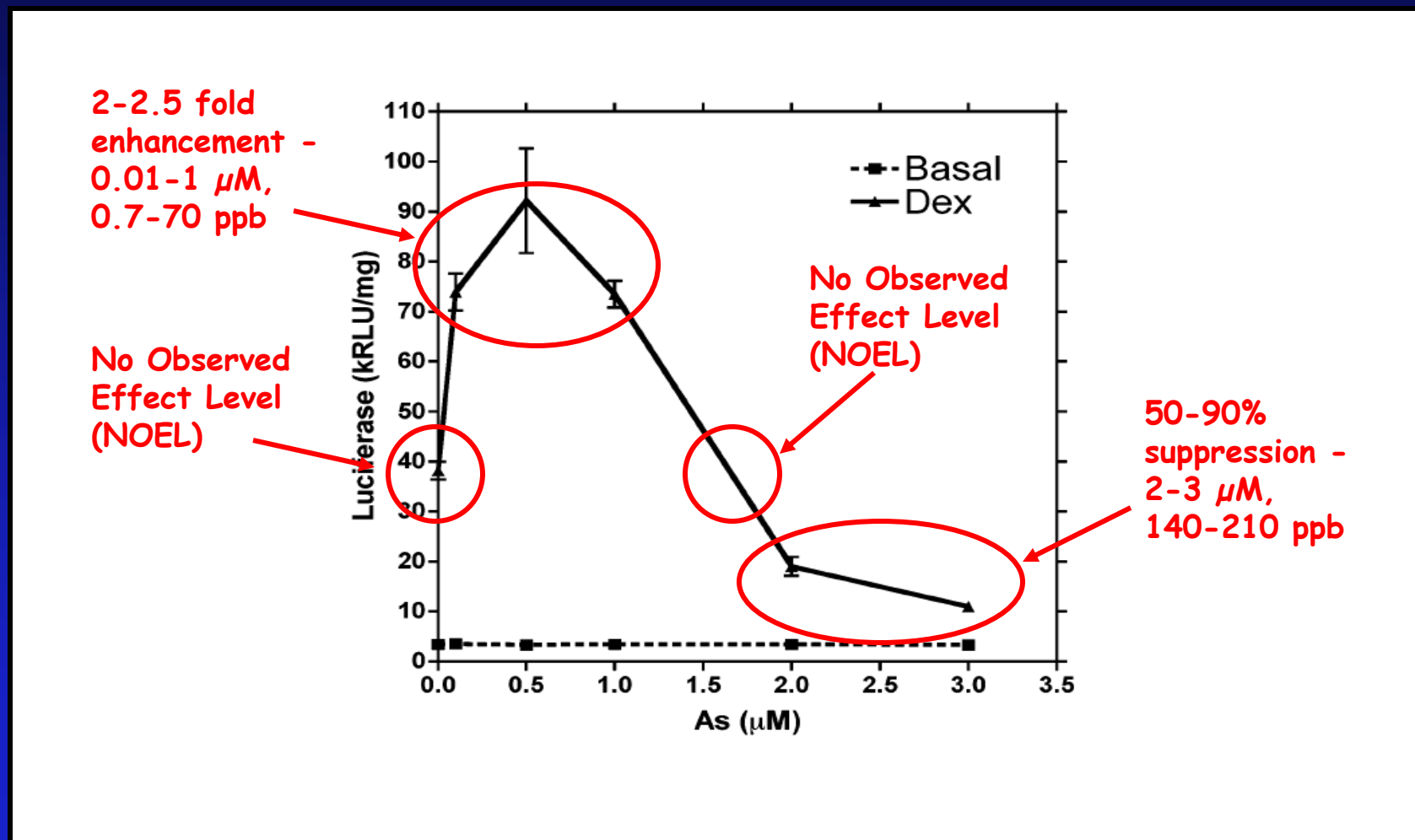
organic Endocrine
Disrupting Chemicals
- EDCs (pesticides, etc.)



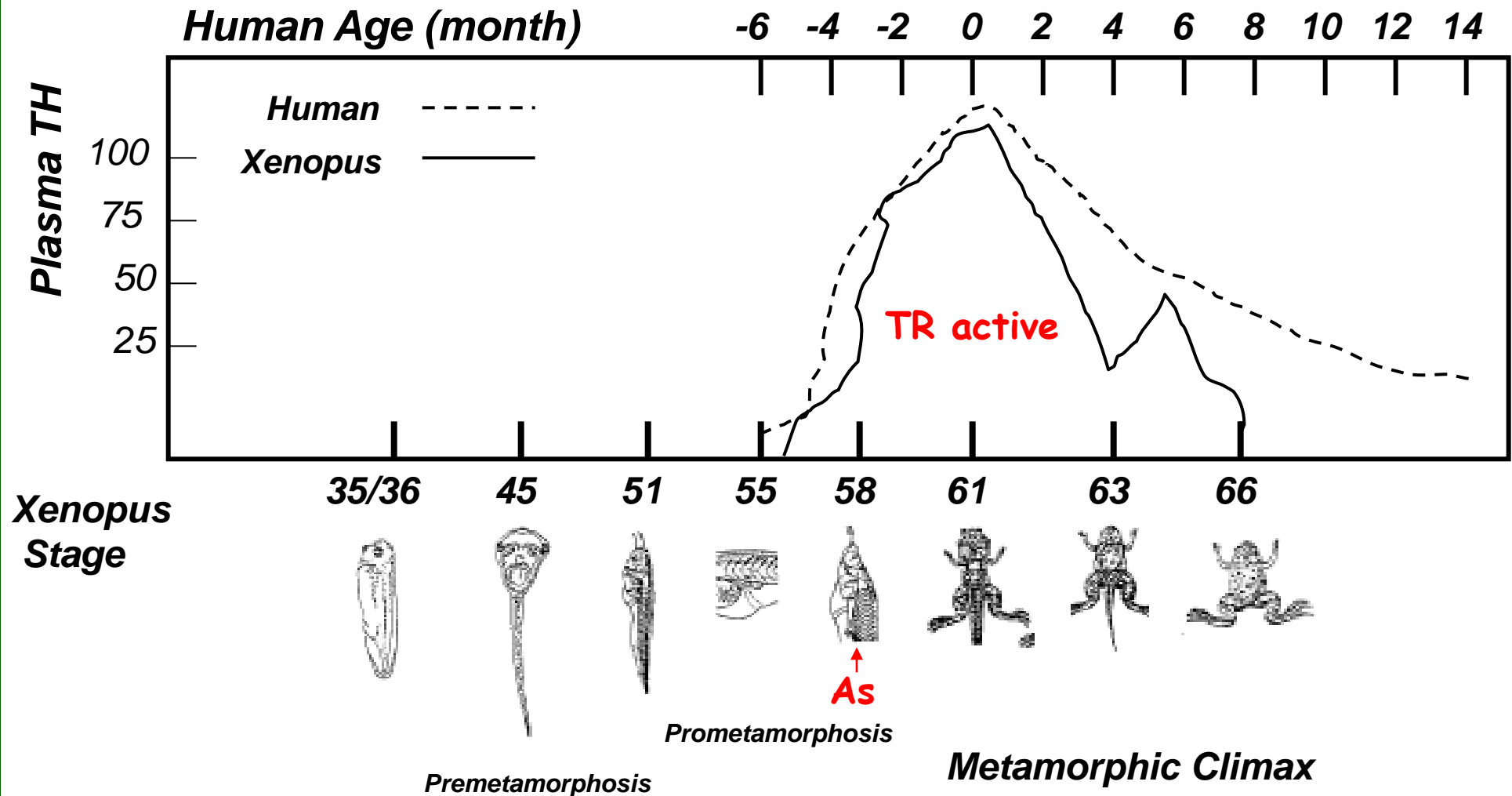
competitive agonists -
mimic hormone, bind to
receptor, activate
receptor

competitive antagonists -
mimic hormone, bind to
receptor, block normal
hormone binding and
activation

Arsenic has opposite effects on steroid receptor function at lower (0.01-1.0 μM) and higher (2-3 μM) doses



Thyroid hormone mediated metamorphosis - *Xenopus*



Effects of arsenic on thyroid hormone-mediated *ex vivo* tail shrinkage in *Xenopus*



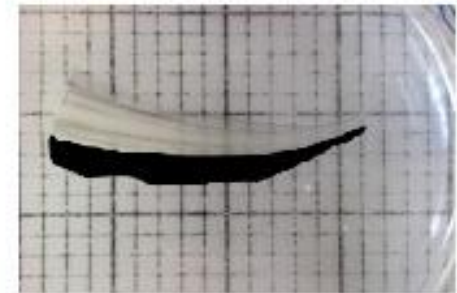
Day 1 - control



T3 only



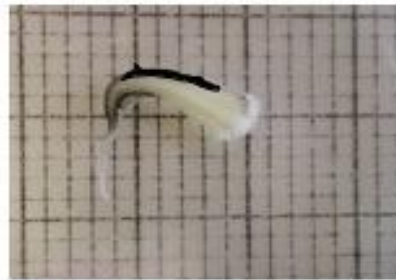
As only



T3+2uMAs



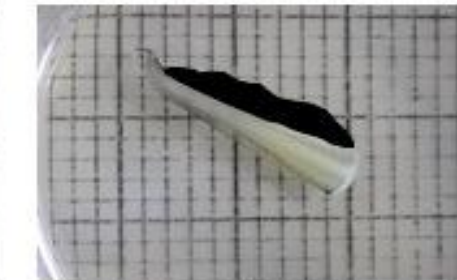
Day 4 - control



T3 only



As only



T3+2uMAs

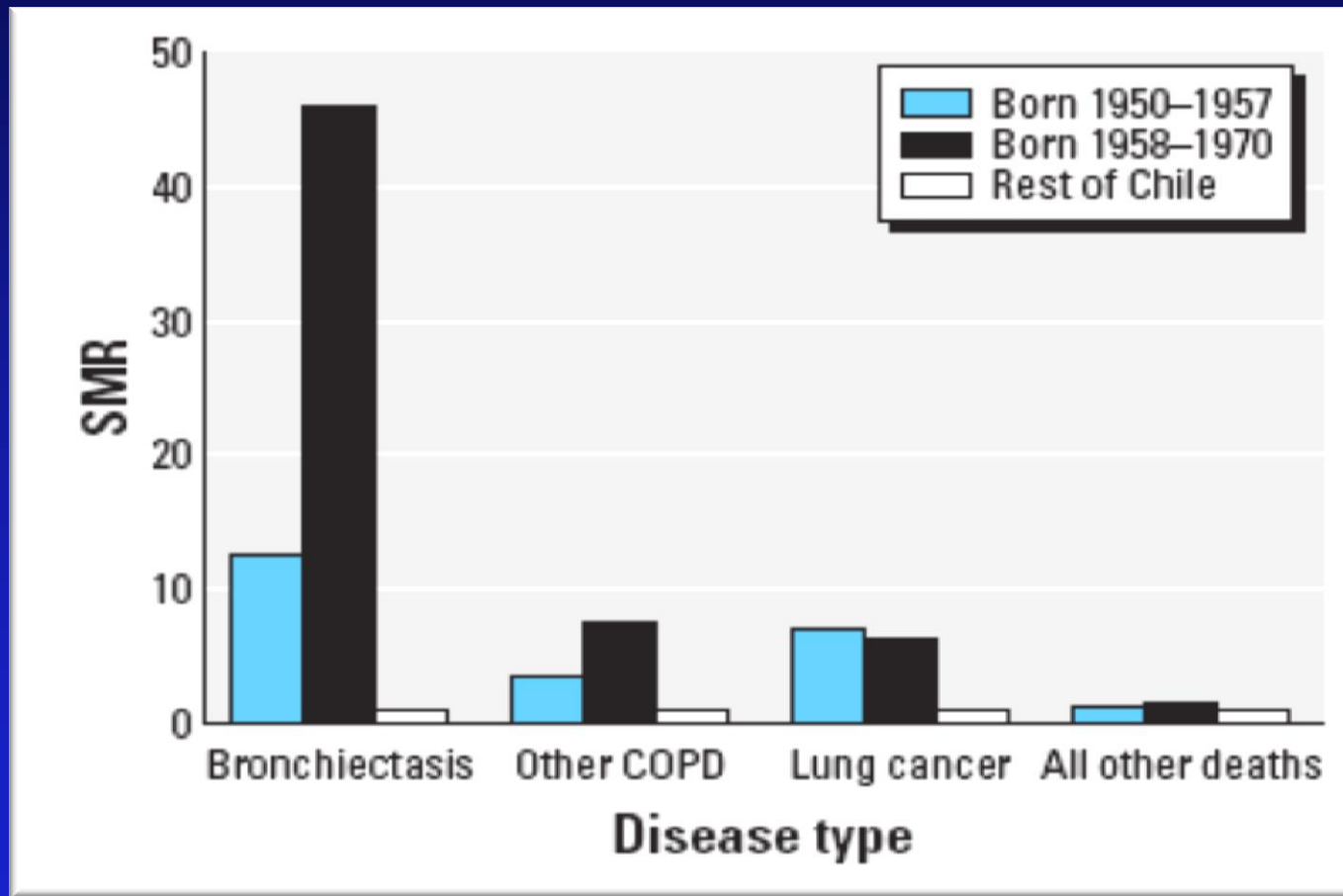
Summary of arsenic as an endocrine disruptor

- Arsenic affects all five steroid hormone receptors:
 - Estrogen Receptor
 - Progesterone Receptor
 - Androgen (Testosterone) Receptor
 - Glucocorticoid (Cortisol) Receptor
 - Mineralocorticoid (Aldosterone) Receptor
- Arsenic affects other nuclear hormone receptors:
 - Retinoic Acid Receptor
 - Thyroid Hormone Receptor
 - PPAR Receptors
- Arsenic enhances hormone signaling at very low doses
- Arsenic suppresses hormone signaling at higher doses

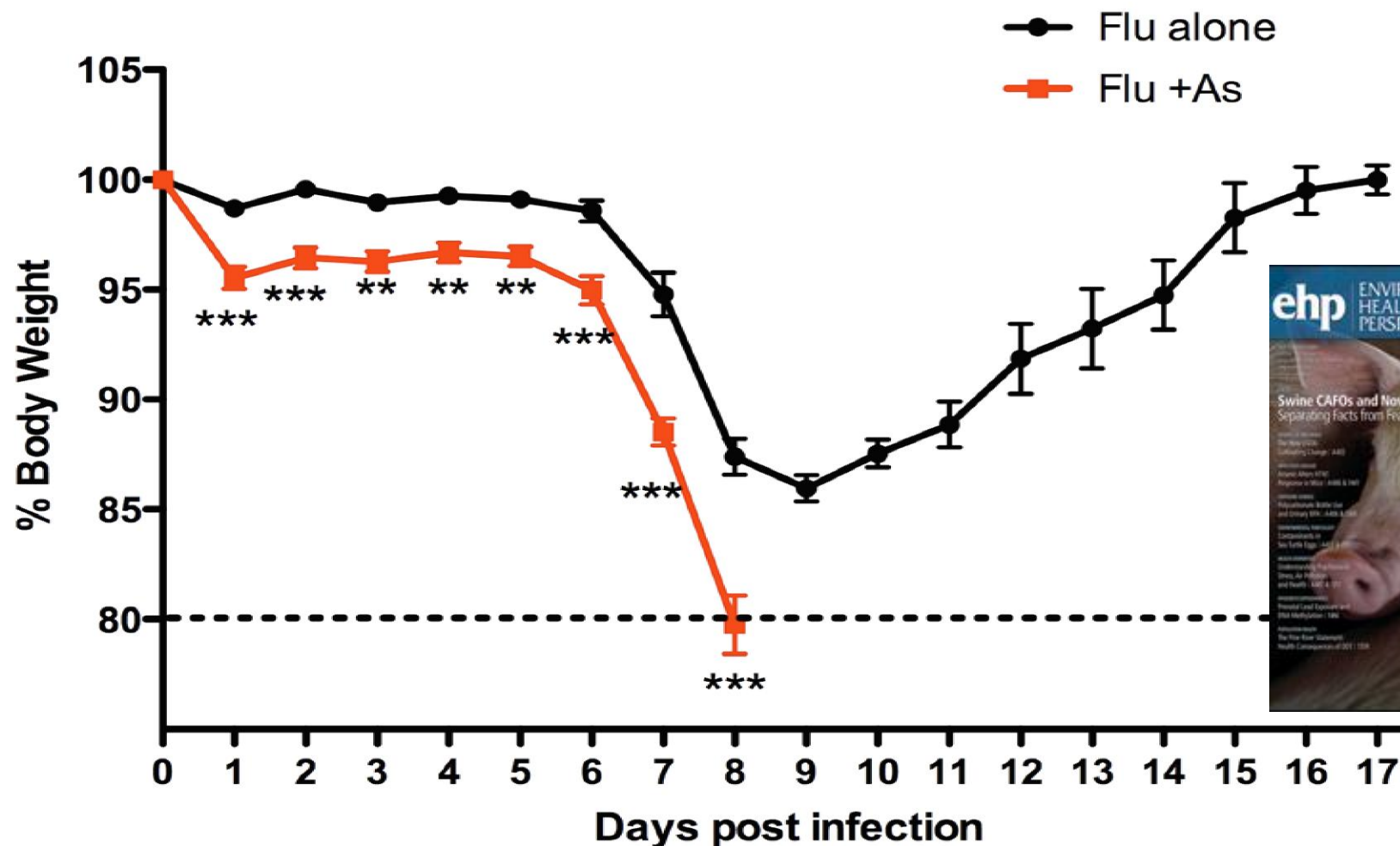
Arsenic and lung disease

- Arsenic exposure is associated with increased risk of:
 - Lung Cancer
 - Bronchiectasis
 - COPD
 - Emphysema
 - Chronic Lung Infections
- Arsenic is unique in increasing lung disease risk via ingestion rather than (or in addition to) inhalation
- Arsenic synergistically increases risk of lung disease from other lung toxicants including tobacco smoke, environmental air contaminants, bacterial and viral infections

Arsenic and long-term risk of bronchiectasis in Region II of Chile



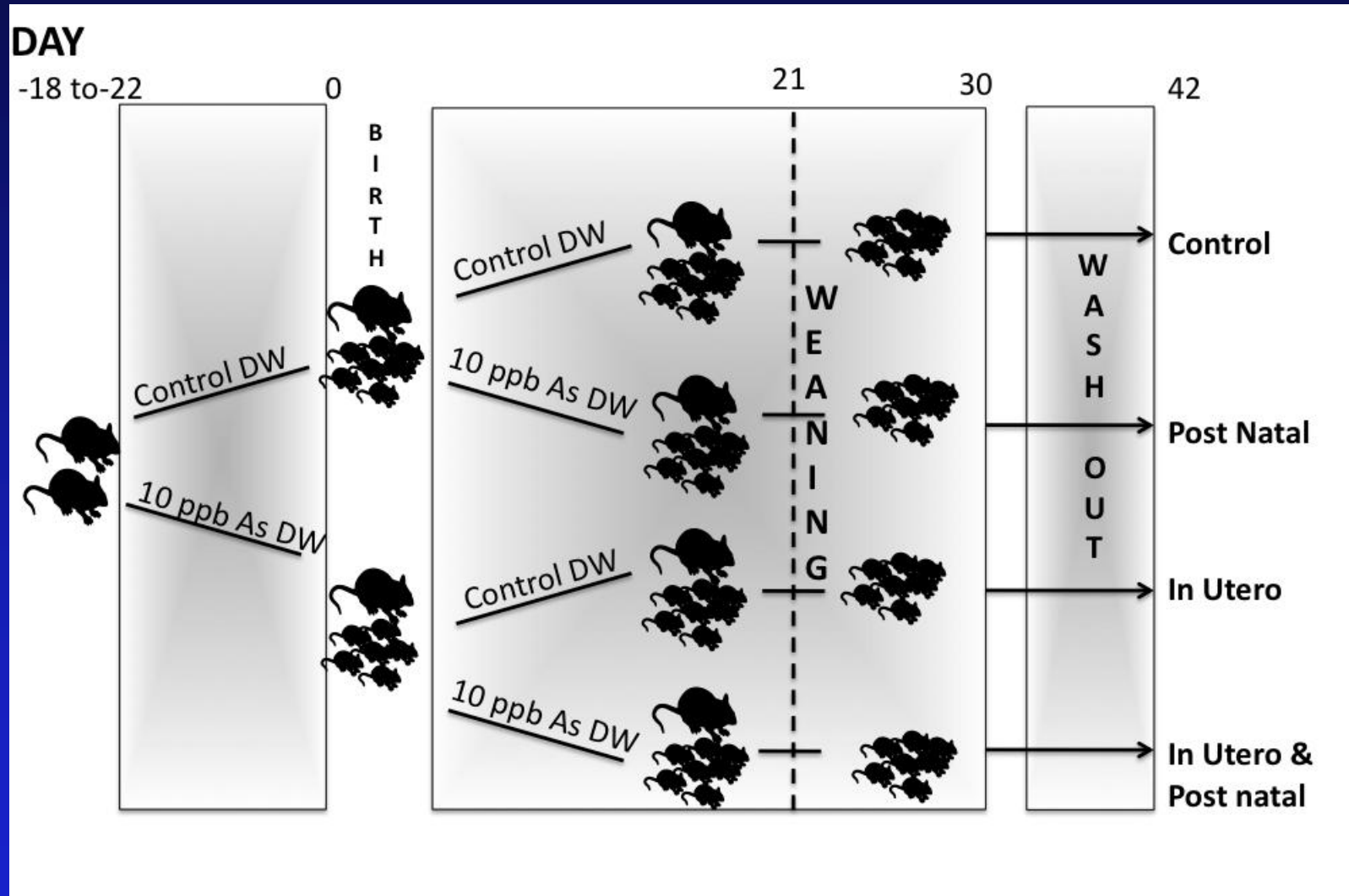
Arsenic in drinking water (100 ppb) increases
H1N1 flu-induced morbidity in mice



Arsenic and metabolic diseases

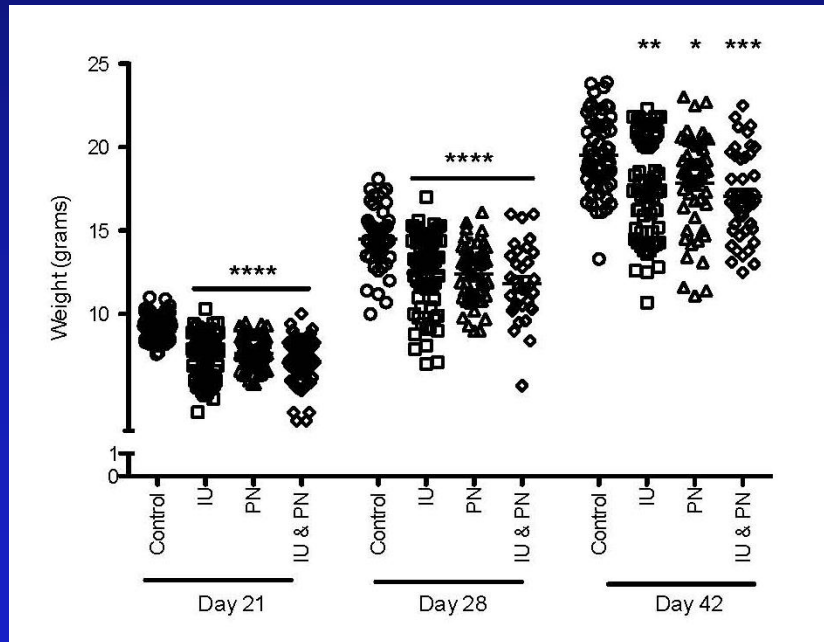
- Arsenic exposure has been associated with:
 - Changes in serum cholesterol and triglycerides
 - Development of type 2 diabetes and other metabolic disorders
 - Lower than normal birth weights
 - Decreases in body weight and growth during early childhood
 - Vascular and cardiovascular disease

Effects of arsenic on mouse fetal and maternal health



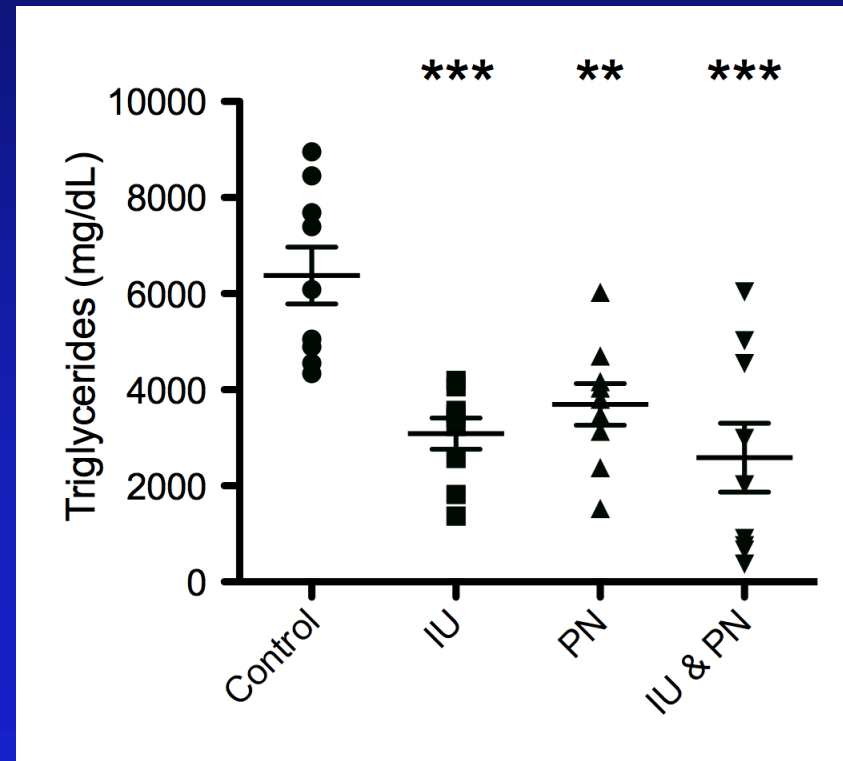
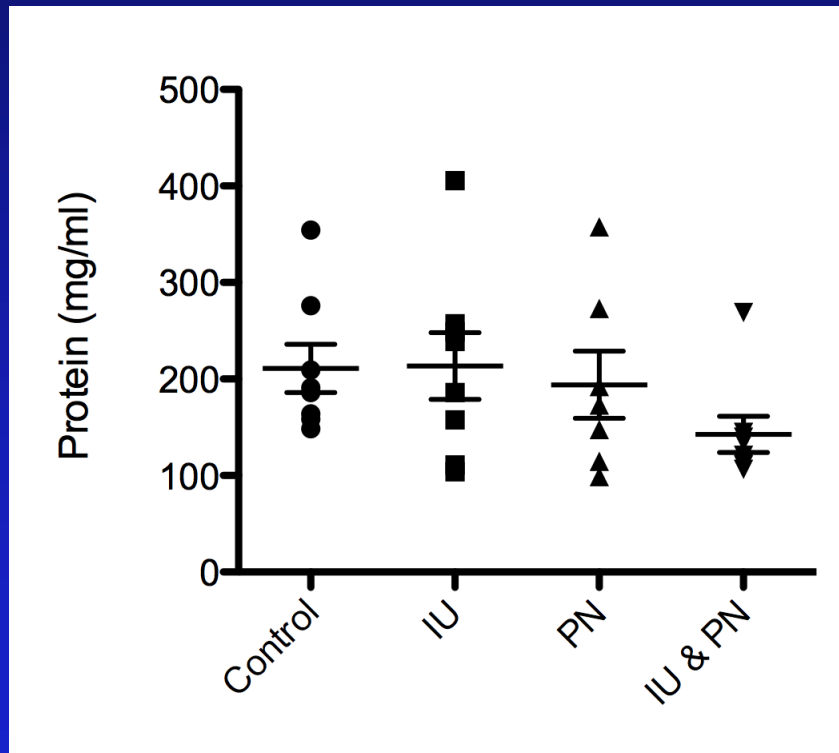
Arsenic at 10 ppb in drinking water affects mouse fetal growth and development

Pregnant C57BL/6J mice were given 10 ppb arsenic in drinking water during the in utero only, post-natal weaning only, or in utero and post-natal periods



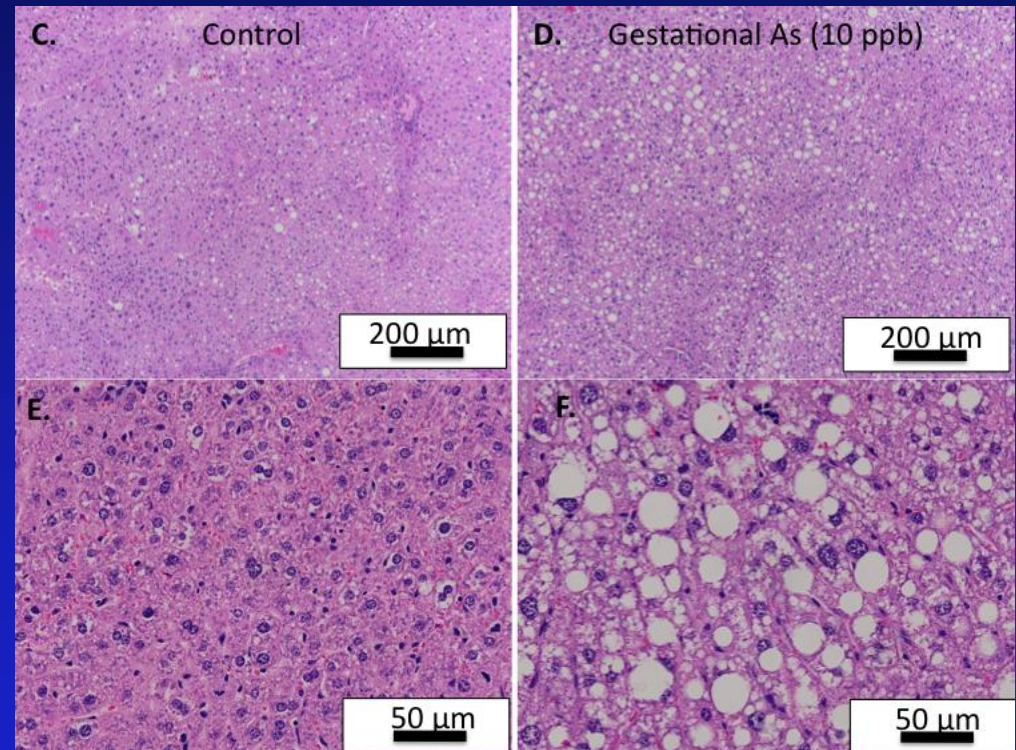
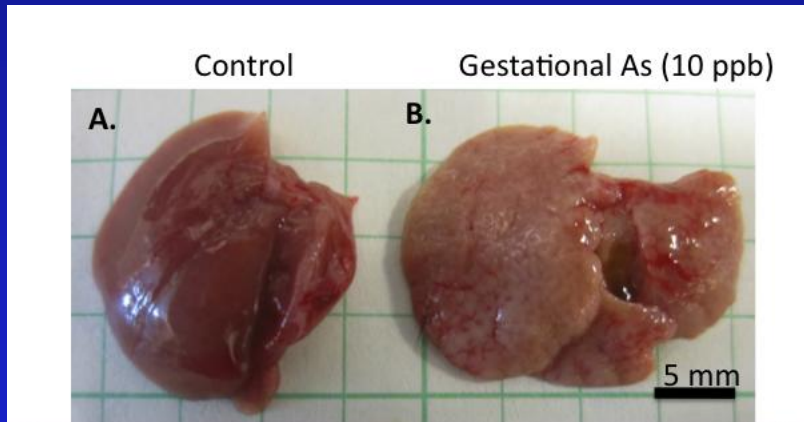
Arsenic at 10 ppb in drinking water affects mouse maternal breast milk nutrients

Pregnant C57BL/6J mice were given 10 ppb arsenic in drinking water during the in utero only, post-natal weaning only, or in utero and post-natal periods



Arsenic at 10 ppb in drinking water causes fatty liver in pregnant mice

Pregnant C57BL/6J mice were given 10 ppb arsenic in drinking water during the in utero only, post-natal weaning only, or in utero and post-natal periods



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